February 13, 2004

Elizabeth K. Hunt
Executive Director
Dimethyl Sulfoxide Producers Association
941 Rhonda Place S.E.
Leesburg, VA 20175

Dear Ms. Hunt:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Dimethyl Sulfoxide posted on the ChemRTK HPV Challenge Program Web site on October 15, 2003. I commend the Dimethyl Sulfoxide Producers Association for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Association advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Dimethyl Sulfoxide

Summary of EPA Comments

The sponsor, the Dimethyl Sulfoxide (DMSO) Producers Association, submitted a cover letter and robust summaries to EPA for dimethyl sulfoxide (DMSO; CAS No. 67-68-5) dated August 12, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on October 15, 2003.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The submitted data for all endpoints are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitted data for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program. The submitted data for biodegradation are inadequate.

2. Health Effects. Adequate data are available for acute, repeated-dose, and developmental toxicity and chromosomal aberrations for the purposes of the HPV Challenge Program. EPA reserves judgement on adequacy of the data submitted for gene mutations and reproductive toxicity endpoints pending receipt of additional information. The submitter needs to address deficiencies in the robust summaries.

3. Ecological Effects. Adequate data are available for fish for the purposes of the HPV Challenge Program. The data submitted for algae and aquatic invertebrates may be acceptable on a weight-of-evidence basis; however, the submitter needs to provide missing information in the robust summaries to allow an independent evaluation. EPA also recommends that values generated by SAR modeling be provided as supporting information.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Dimethyl Sulfoxide Challenge Submission

Test Plan

General

In lieu of a test plan the submitter stated in the cover letter that no testing was necessary.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The submitted data for all endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The submitted data for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program.

Biodegradation. The submitted Japanese MITI test was run for only two weeks rather than the four weeks required in OECD 301C. Since dimethyl sulfoxide might have passed a four-week test, the submitted data are inadequate and the submitter needs to perform the test according to OECD TG 301.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for acute, repeated-dose, and developmental toxicity and chromosomal aberrations for the purposes of the HPV Challenge Program. EPA reserves judgement on the adequacy of the data submitted for gene mutations and reproductive toxicity endpoints pending receipt of additional information. The submitter needs to address deficiencies in the robust summaries.

Repeated-dose toxicity. The submitter needs to include a robust summary for a 13-week repeated-dose inhalation study in rats (OECD TG 413) submitted for the reproductive toxicity endpoint.

Genetic toxicity (gene mutations). Adequacy of the data submitted for this endpoint cannot be determined because none of the robust summaries provides information on positive and negative controls. The submitter needs to provide this information, which is required to evaluate the validity of the assays, in addition to addressing deficiencies noted in the Specific Comments section.

Reproductive toxicity. A robust summary for a 13-week repeated-dose inhalation study in rats (OECD TG 413) submitted for this endpoint indicates that the highest concentration is a NOAEL for reproductive parameters (histopathology, estrous and sperm effects), and no robust summary is provided for this study under the repeated-dose toxicity section to report whether or not the highest concentration is also a NOAEL for systemic toxicity. Additional omissions include the group size, the method for generating the test atmosphere, the maximum attainable concentration, and the results for systemic toxicity. Adequacy of the study for the reproductive toxicity endpoint cannot be determined pending receipt of the missing information in the robust summaries.

Ecological Effects (fish, invertebrates, and algae)

The studies for invertebrates were shorter than the OECD Guideline-required duration of 48 hours, and the data submitted for algae were generated in studies that were shorter or longer than the OECD Guideline-required duration of 72 or 96 hours. However, the data for these two endpoints may be acceptable on a weight-of-evidence basis. The submitter needs to provide missing information in the robust summaries so that an independent evaluation can be made. In addition, EPA recommends that values generated by SAR modeling be provided to support the conclusion of low toxicity.

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity. Robust summaries for acute oral toxicity studies in rats and mice are missing a few pieces of information, including the method for calculating the LD_{50} and the results for clinical signs and mortality by sex and exposure level. In addition, the summaries do not indicate whether body weights were monitored.

Repeated-dose toxicity. Missing information in a robust summary for an 18-month oral study in rhesus monkeys includes mortality by sex and the reference citation. In addition, the reported NOAEL (3300 mg/kg bw) and LOAEL (9900 mg/kg bw) do not match the test doses provided (990-2970-8910 mg/kg) in the summary.

Genetic toxicity (chromosomal aberrations). A robust summary for an *in vivo* cytogenicity assay (chromosomal aberration) in rats does not adequately describe time of exposure and criteria for evaluating results. In addition, an attachment tabulating the percentage of aberrant cells per animal per dose level (Kapp table 1.tif) is missing.

Developmental toxicity. A robust summary for a developmental toxicity study in rats by oral on gestational days 6-15 (OECD TG 414) omits the vehicle (if used), the magnitude of body weight effects, and statistical analysis.

Ecological Effects

Algae. The submitter needs to provide, where missing, the pH, water hardness, and temperature for as many studies as possible, particularly the 96-hour algal study on *Skeletonema costatum*.

Invertebrates. The submitter needs to provide missing pH, water hardness, temperature, dissolved oxygen, and other pertinent information.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.